REMARKS

Prior to the present amendment, claims 23-29, 31, 33, and 34 were pending. A restriction requirement was issued on September 6, 2006. In response, applicant elected claims drawn to a species of (a) the method carried out *in vivo*, (b) introducing a nucleic acid that encodes the polypeptide, (c) wild-type T box sequence of TBX5 capable of binding to both the major and minor grooves of target DNA, (d) wherein the cell into which the polypeptide is introduced is a malignant cell. Applicant elected the following claims as readable on the elected species: 23, 25, 26, 28, 29, 31, and 33.

By this present amendment, applicants have amended claim 23, and canceled claims 24, 27, and 34. Accordingly, claims 23, 25, 26, 28, 29, 31, and 33 are under consideration.

Interview

Applicants wish to thank Examiner Ungar for the courtesy of a telephone interview with applicant's representatives, Irving N. Feit and the undersigned, on July 19, 2007. During the telephone interview, the rejections presented in the office action of April 30, 2007 were discussed. Applicant's representatives greatly appreciate the clarification and explanations provided by Examiner Ungar during the interview. The discussion below contains a summary of the interview.

Objections to the Specification

On page 1 of the office action, the Examiner objected to the specification for containing spelling errors. In response, applicant corrected the spelling error found on page 4 of the specification as filed.

In addition, the Examiner objected to figures 2 and 3 and the brief description of the drawings. According to the Examiner, there is no legend on the drawings or a definition in the description of what the lines on the graph represent.

With respect to figure 2, applicant directs the examiner's attention to the paragraph bridging pages 28 and 29 of the specification as filed, i.e. paragraph [0102], which explains what the lines on the graph of figure 2 represent. For example, D17 cells infected with TBX5-CXIZ are represented by a solid line and ■. With respect to figure 3, applicant directs the Examiner's attention to page 32, paragraph [0110], specification as filed. This cited paragraph explains what the solid and open bars represent. Accordingly, the specification as filed provides a legend for the graphs of figures 2 and 3. Applicant respectfully requests that the Examiner reconsider and withdraw the objections.

Rejection under 35 U.S.C. § 112, first paragraph– Written Description

On page 2 of the office action, the examiner rejects claims 23, 25, 26, 28, 29, 31, and 33 as allegedly lacking an adequate written description. According to the Examiner, the specification provides an adequate written description of two species of a nucleic acid encoding a polypeptide comprising a translated 5' T-box sequence of TBX5. The specification, however, allegedly does not provide the complete or partial structure, or physical or chemical characteristics, of any introduced nucleic acid encoding a polypeptide comprising a translated 5' T-box sequence of TBX5.

During the interview, Examiner Ungar explained that upon further review of the application, limiting the claims to the two disclosed species is not necessary to overcome the present rejection. The Examiner further explained that amending the claims to recite "a translated human 5' T-box sequence of TBX5" would suffice to overcome the rejection.

Applicants representatives wish to thank Examiner Ungar for clarifying the rejection and suggesting a claim limitation. By this amendment, applicant amended the claims in accordance with the examiner's suggested language. Applicant respectfully requests the examiner to reconsider and withdraw the rejection under 35 USC § 112, first paragraph.

Rejection under 35 U.S.C. § 112, second paragraph–Indefiniteness

On page 11 of the office action, the examiner rejects claims 23, 25, 26, 28, 29, 31, and 33 as allegedly being indefinite for the following recitation: "a polypeptide comprising a translated 5' T-box sequence of TBX5 capable of binding to the major groove of target DNA."

During the interview, Examiner Ungar explained that the language of claim 23 is confusing because the claim appears to require a nucleic acid sequence that is capable of binding to the major groove of target DNA. She notes, however, that the polypeptide and not the nucleic acid sequence is required to be capable of binding to the major groove of target DNA. Examiner Ungar suggested that claim 23 be clarified by rearranging the claim language.

Accordingly, applicant has amended claim 23 by rearranging the claim language, so as to clarify that the polypeptide is capable of binding to the major groove of target DNA. Applicant respectfully requests the examiner to reconsider and withdraw the rejection of the claims.

Rejection under 35 U.S.C. § 112, first paragraph–Enablement

On page 7 of the office action, the examiner rejects claims 23, 25, 26, 28, 29, 31, and 33 as allegedly lacking enablement for a method of inhibiting proliferation of a malignant cell *in vivo*. The method comprises introducing into the cell a nucleic acid that encodes a polypeptide comprising a translated T-box sequence of TBX5. On page 9 of the office action, the Examiner acknowledges that the specification discloses *in vitro* infection of D17 canine osteosarcoma cells with SEQ ID NO: 1, or a truncated mutant isoform thereof, resulted in slower proliferation of D17 cells over controls. According to the Examiner, the teaching of the specification cannot be extrapolated to the scope of the claims because the art recognizes the unpredictability, pitfalls, and inherent limitations of cancer therapy discovery based on *in vitro* studies.

In response, applicant wishes to direct the Examiner's attention to examples 12 and 13, which demonstrate that TBX5 overexpression *in vivo* has an inhibitory effect on cell proliferation. In particular, the examples demonstrate that an overexpression of TBX5 in chick embryo hearts inhibited proliferation and resulted in hearts 15% smaller than the controls. See, for example, paragraph [0107] on page 30 of the specification as filed.

During the interview, Examiner Ungar acknowledged that the application discloses *in vivo* studies performed in normal chick embryos. However, she stated that in order to overcome the enablement rejection, she would like to see additional objective evidence showing a "nexus" between the chick embryo studies and a recognized animal model, e.g., in a mouse. She explained that the nexus should evidence chick embryo studies as being predictive of studies in the animal model.

In response, applicant submits an abstract that states that "a good correlation" exists between chick embryo assays and nude mice for measuring metastatic properties of different cell types from several species. See Chambers, et al., "Comparison of metastatic properties of a variety of mouse, rats, and human cells in assays in nude mice and chick embryos," *In Vivo*, July-Aug; 4(4): 215-219 (1990), a copy of which is attached as Exhibit A. The Chambers, et al. article further states that the chick embryo assay is a useful alternative host for metastasis studies and that it correlates well with assays using nude mice.

In addition, applicant submits a reference that discloses that mouse models of cancer have consistently been used to qualify new anticancer drugs for study in human clinical trials. One of the "most used" models is immunodeficient mice, i.e. nude mice. See Sausville, et al. "Contributions of Human Tumor Xenografts to Anticancer Drug Development," *Cancer Res.*, 66(7), pp. 3351-3354 (2006), a copy of which is attached as Exhibit B.

Based on the above cited references, one skilled in the art would have confidently made a connection or "nexus" between the inhibition of cell proliferation studies performed in chick embryos *in vivo* and those performed in a recognized animal model system, e.g., mice. More specifically, based on Chambers, et al., a good correlation exists between the two assay systems. Based on the Sausville, et al. article, the use of nude mice constitutes one of the most common models of cancer for qualifying new anticancer drugs for human clinical trials.

Moreover, a well-accepted intersection exists between embryogenesis and oncogenesis. See, for example, the following abstracts. A copy of each abstract is attached as Exhibit C.

- Katoh, "Networking of WNT, FGF, Notch, BMP, and Hedgehog Signaling Pathways during Carcinogenesis," Stem Cell Rev. 2007;3(1):30-8 (review that highlights a commonality of growth regulatory pathways in development, stem cell biology, and cancer).

- McDonnell, et al. "Vascular leakage in chick embryos after expression of a secreted binding protein for fibroblast growth factors, " Lab Invest. 2005 Jun;85(6):747-55 (chick experiment with relevance to cancer).

- Zervas, et al. "Classical embryological studies and modern genetic analysis of midbrain and cerebellum development," Curr Top Dev Biol. 2005;69:101-38 (review of intersection of embryogenesis and cancer and chick embryo models).

- Lee, et al. "Embryonic expression patterns of the mouse and chick Gas1 genes," Mech Dev. 2001 Mar;101(1-2):293-7 (study investigating an oncogene that has relevance in cancer and growth regulation in mouse and chick development).

- Galli, et al. "Differential inhibition of Wnt-3a by Sfrp-1, Sfrp-2, and Sfrp-3,"Dev Dyn. 2006 Mar;235(3):681-90 (relevance of critical regulators of chick development to embryogenesis and cancer).

- Takaha, et al. "Expression of gicerin in development, oncogenesis and regeneration of the chick kidney," Differentiation. 1995 Jun;58(5):313-20 (study of the intersection between chick embryonic development and tumor formation).

For the foregoing reasons, the cited references individually or in combination fail to obviate the claimed invention.

In view of the foregoing amendments and remarks, entry of the amendments to, and favorable consideration of, the claims are respectfully requested. If the examiner has any questions or concerns regarding this amendment, she is invited to contact the undersigned at the telephone number listed below.

If any additional fees are due or any overpayment has been made in connection with this paper, please charge or credit our Deposit Account No. 08-2461 for such sum.

Respectfully submitted,

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